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**Patentanmeldung Nr.    Patent application No.    Demande de brevet n°**

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Der Präsident des Europäischen Patentamts;  
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets  
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Composition for improving skin, hair and coat health

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### **Composition for improving skin, hair and coat health.**

5 The present invention pertains to a composition for preventing, decreasing and/or treating skin and hair/coat disorders or damages, such as is effected by inflammatory reactions, environmental factors, ageing or cancer. In particular, the present invention relates to the use of flavanones compounds or their derivatives in nutritional, cosmetic or pharmaceutical compositions for improvement of human or pet animal skin and coat conditions.

### **Background of the invention**

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The most prominent epithelial tissue in living beings is the skin, which represents the largest organ in the organism. The system of skin integument, which comprises the epidermis, dermis and the stratum corneum, correlates with those of internal organs and concurrently interacts with the surroundings. Being the interface between the environment and organism itself, the skin is heavily influenced by external factors and also variable parameters of the organism's inner system. The skin's regulative mechanisms need, therefore, always be active to induce systemic changes necessary to maintain normal pathological events concerning skin integument morphology and activities.

15 20 A great deal of processes assuring the adequate consumption of increased affluence of energetic and plastic substances according to the skin's needs become guarantors of morphological and functional stability of skin structures. So, the state of integuments determines the realization of metabolic processes necessary for skin cell viability and activity leading to the presence of healthy skin peculiarities such as barrier function, elasticity, turgor properties, humidity, pigmentation etc..

25 30 During the lifetime of a living being different signs, characteristic of ageing, appear on the skin or hair, with the principal clinical signs being the appearance of fine lines and deep wrinkles which increase or are accentuated with age, loss of hair, reduced hair density, glossiness, color, oilness, fiber diameter, etc....

These signs of ageing are even promoted by exposure of the skin and hair to exogenous influences, such as e.g. UV-radiation, pollutants, free radicals or chemical substances.

5 In the art several means have been proposed to prevent destructive effects of environment or ageing on skin epithelial cells. For example, means to prevent skin deterioration or ageing is to provide compounds scavenging free radicals. In this respect EP 0 761 214 discloses singlet oxygen quenchers comprising aniline derivatives and difurfuryl amine derivatives, which are reported to reduce the oxidative stress to the skin.

10 Although there is a great diversity of active compounds for ameliorating skin and hair or coat health, there still exists a need in the art to provide new active compounds. In particular, an object of the present invention is to provide compositions that may be used over a long period of time by humans or pets, and susceptible to be provided in the form of a nutritional supplement, for example a nutritional composition.

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### Summary of the invention

20 In a first aspect, the present invention relates to a nutritional, cosmetic or pharmaceutical composition for human or pets, which contains as active compound, at least one flavanone compound or its derivatives, or a mixture thereof, in an efficient amount to prevent, treat or alleviate skin, hair and/or coat disorders and ameliorate skin, hair and coat health.

25 In another aspect, the invention provides the use of at least one flavanone or its derivatives or mixtures thereof, as active compound in the preparation of a nutritional, cosmetic or pharmaceutical composition intended for preventing or treating skin, hair and/or coat disorders, thus ameliorating skin health conditions in humans or pets.

30 The composition according to the present invention may be in the form of a complete nutritional formula, a dietary supplement to be orally administered to a human or an animal, or a compound for pharmaceutical use.

NO 7702/EP

Administering to a human or pet animal, a food composition as described above, results in an improved skin health, e.g. on photoprotection, hydration, dryness, firmness, thickness, elasticity, oiliness, regular pigmentation, immunity or hair and coat health, e.g. improving hair and coat gloss, hair density, color, oilness, ameliorating hair fibre diameter, sebum production, glossiness and preventing hair and coat loss. Also, the composition according to the present invention is administered to a human or an animal, for ameliorating antioxidant status, barrier function, to prevent or modulate oxidative status, sebum production or composition, or to reduce signs of ageing. It also helps to reduce risks of cancer or inflammation.

10

#### Detailed description of the invention

According to the first object, the invention provides a nutritional, cosmetic or pharmaceutical composition for human or pets, which contains as active compound, at least one flavanone compound or its derivatives, or a mixture thereof, in an efficient amount to prevent, treat or alleviate skin, hair and/or coat disorders or damages and thus ameliorate skin, hair and coat health.

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The flavanone compounds of interest are natural glycosides that can be found principally in fruits from the genus Citrus, such as orange, lemon, bitter orange, grapefruit, for example or in a lesser extend in other vegetables. They are present in majority in the peel of the fruit, but also in large amounts in the pulp and thus also in citrus fruit juice. The compounds according to the present invention may be isosacuranetin, naringin, hesperidin, or eriodictyol, poncirin, neoeriocitrin, for example, and their derivatives selected from their aglycone forms, chalcone forms, glycosylated forms or methylated forms. Also, their sulfated or glucuronidated forms which are found as product of metabolism in blood are used.

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In a last aspect, derivatives may be obtained by several processes known in the art, such as enzymatic treatments. For example, glucose-7-hesperetin is prepared by rhamnosidase or hesperidinase treatment.

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NO 7702/EP

The flavanone compound or derivatives according to the invention may be included in any composition suitable for administering the substance to an individual, in particular a food composition, a cosmetic composition or a pharmaceutical composition.

5

In a preferred embodiment, a food composition for human consumption is prepared. This composition may be a nutritional complete formula, a dairy product, a chilled or shelf stable beverage, soup, a dietary supplement, a meal replacement, and a nutritional bar or a confectionery. The composition may be selected from the group consisting of milk, or  
10 fermented milk products, such as e.g. yogurt, curd, cheese, milk based fermented products, ice-creams, milk based powders, infant formulae, cereal products and fermented cereal based products, beverages, mineral water, chocolate or pet food containing at least a flavanone compound or one of its derivatives. The nutritional supplement for oral administration may be in capsules, soft capsules, tablets, pastes or pastilles, gums, or drinkable solutions or emulsions.  
15 Methods for preparing them are common knowledge.

As described above, flavanones compounds are found naturally in Citrus fruits, in particular in oranges, lemons and grapefruit, in their peel or pulp. Accordingly, in a first aspect, the nutritional composition may be in the form of a juice of such fruits or in the form of a  
20 concentrate. Thus, the nutritional composition may be in the form of any food product, in particular any beverage, citrus juice or any other extract from peel or pulp of citrus fruits.

In another embodiment, a usual food product may be enriched with the flavanones, preferably in the form of citrus extract. For example, a fermented milk, a yoghurt, a fresh  
25 cheese, a renneted milk, a confectionery bar, breakfast cereal flakes or bars, drinks, milk powders, soy-based products, non-milk fermented products or nutritional supplements for clinical nutrition. In particular, a process for preparing an extract enriched if flavanones, in particular hesperidin, from orange and lemon is described in US N02,400,693 and US 2,442,110, respectively.

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NO 7702/EP



According to a further aspect, flavanones compounds to be included in the specification may be synthetically produced.

A nutritional composition according to the present invention may comprise the flavanone compounds, its derivatives or mixtures thereof in an amount adapted to a daily oral administration, and of from about 0.01 mg to 1g, preferably from about 0.1 mg to 800 mg, more preferably from 10 mg to 800 mg of the aglycone equivalent of the flavanone compound.

10 The flavanones according to the invention may be used either alone or in association with other active compounds such as vitamin C, vitamin E (tocopherols and tocotrienols), carotenoids (carotenes, lycopene, lutein, zeaxanthine, beta-cryptoxanthine, etc.) ~~ubiquinones~~ (e.g. CoQ10), catechins (e.g. epigallocatechin gallate), coffee extracts containing polyphenols and/or diterpenes (e.g. kawheol and cafestol), extracts of chicory, ginkgo biloba extracts, 15 grape or grape seed extracts rich in proanthocyanidins, spice extracts (e.g. rosemary), soy extracts containing isoflavones and related phytoestrogens and other sources of flavonoids with antioxidant activity, fatty acids, e.g. n-3 fatty acids, prebiotic fibers, probiotic microorganisms, taurine, resveratrol, aminoacids, selenium and precursors of glutathione, for example.

20

In another embodiment, a pharmaceutical compositions can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, compositions are administered to a patient already suffering from a disease, as described herein under, in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. An amount 25 adequate to accomplish this is defined as "a therapeutically effective dose". Amounts effective for this will depend on the severity of the disease and the weight and general state of the patient.

In prophylactic applications, compositions according to the invention are administered to a patient susceptible to or otherwise at risk of a particular disease. Such an amount is defined to be 30 "a prophylactic effective dose". In this use, the precise amounts again depend on the patient's

NO 7702/EP

state of health and weight. Preferably, for humans the pharmaceutical composition according to the present invention comprises an amount of flavanone compounds, its derivatives or mixture thereof as described above, for a daily administration, from about 0.01 mg to 500 mg. When administered daily to pets, the composition may comprise from 1 mg et 500 mg of the aglycone equivalent of flavanone compounds.

The compounds of the invention are preferably administered with a pharmaceutical acceptable carrier, the nature of the carrier differing with the mode of administration, for example parenteral, intravenous, oral and topical (including ophthalmic) routes.

10

It will be appreciated that the skilled person will, based on his own knowledge select the appropriate components and galenic form to target the active compound to the skin or hair taking into account the route of administration which may be by way of injection, topical application, intranasal administration, administration by implanted or transdermal sustained release systems, and the like.

15

The objective substance may also be formulated in a cosmetic product, such as lotions, shampoos, creams, sun-screens, after-sun creams, sun-blocker, anti-ageing creams and/or ointments. It will be appreciated that the present cosmetic products will contain a mixture of different ingredients known to the skilled person, ensuring a fast penetration of the objective substance into the skin and preventing degradation thereof during storage.

20

It will be understood that the concept of the present invention may likewise be applied as an adjuvant therapy assisting in presently used medications. Since the compounds of the present invention may easily be administered together with food material special clinical food may be applied containing a high amount of the objective substances. It will be clear that on reading the present specification together with the appending claims the skilled person will envisage a variety of different alternatives to the specific embodiments mentioned herein.

25

In principle, the compounds according to the present invention may be used for the treatment

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NO 7702/EP

and/ or prevention of damages in the skin which are produced by a stress situation e.g. by means of a chemical, biological or a physical stress, e.g. by exposure to oxidants or carcinogens, exposure to bacteria, viruses, fungi, lipids derived from surrounding cells and/or microbes, or exposure to UV-irradiation.

5

Consequently, the substances and/or compositions according to the present invention may be utilized for treating and or preventing damages of the skin, in particular actinic and ageing damages of the skin such as dryness, actinic keratoses, irregular pigmentation (notably comprising freckling, lentigines, guttate hypomelanosis and persitent hyperpigmentation),  
10 wrinckling (notably comprising fine surface lines and deep furrows), stellate pseudoscars, elastosis, inelasticity, telangiectasia, venous lakes, purpura, comedones, sebaceous hyperplasia, acrochordon, cherry angiogema, seborrhea, keratosis, lentigo, basal cell carcinoma and squamous cell carcinoma, skin burning and/or blistering, epidermal hyperplasia, inflammation, immune suppression, and cancer, e.g. non-melanoma and  
15 melanoma skin cancers. They have also particular benefits on hair and coat, such as an improved hair or coat density, fiber diameter, color, oilness, glossyness, sebum production and a helps to prevent hair or coat loss.

The effect of a food supplementation in flavanones compounds or its derivatives according to  
20 the present invention, on skin of humans or pets, can be measured by using conventional methods including minimal erythemat dose (MED), colorimetry, transepidermal water loss, DNA repair (e.g.p.53), measure of interleukines and proteoglycans production, or collagenase activity, barrier function or cell renewal.

25 The following examples illustrate the invention in more detail without restricting the same thereto.

**Example 1 : mineral water supplemented with flavanone**

30 A mineral water is prepared by adding hesperetin-7-glucose, in an amount of 0.01 mg to 200

NO 7702/EP

mg per liter, estimating that the average consumption is of about 1 liter per day.

### Example 2: Cosmetic for oral administration

5 A composition in the form of a hard capsule has the following formulation:

Compound	mg per capsule
Hesperidine (hesperetin equivalent)	250
<b>Excipient for the core</b>	
Cellulose microcristalline	70
Encompress <sup>TM</sup>	60
Stéarate de Magnesium	3
Silice colloïdale anhydre	1
<b>Agent d'enrobage</b>	
Gomme laque	5
Talc	61
Saccharose	250
polyvidone	6
Dioxyde de titane	0.3
Agent de coloration	5

The composition can administered to the individual in an amount of 2 to 3 capsules daily.

### 10 Example 3: Canned Pet food and supplement

A mixture is prepared from 73 % of poultry carcass, pig lungs and beef liver (ground), 16 % of wheat flour, 7 % of water, 2 % of dyes, flavours, vitamins, and inorganic salts. This mixture is emulsified at 12°C and extruded in the form of a pudding which is then cooked at 15 a temperature of 90°C. It is cooled to 30°C and cut in chunks. 45 % of the chunks are mixed with 55 % of a sauce prepared from 98 % of water, 1 % of dye and 1% of guar gum. Tinplate cans are filled and sterilized at 125°C for 40 min.

As a supplement to be mixed with the pet-food before serving, additional packaging in sachet

NO 7702/EP

form with 50 mg of hesperetin equivalent, in the form of Citrus extract is provided. This is supplied as a supplement with removably attached to the can, together with feeding directions.

**Example 4: Functional food**

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A food supplement was prepared by mixing or blending fructooligosaccharide with inulin in the proportions by weight of about 70% fructooligosaccharide to about 30% inulin and adding 500 mg of hesperetin equivalent. The resulting prebiotic mixture may be added or blended with any suitable carrier, for example a fermented milk, a yogurt, a fresh cheese, a renneted milk, a confectionery bar, breakfast cereal flakes or bars, a drink, milk powder, soy-based product, non-milk fermented product or a nutritional supplement for clinical nutrition.

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NO 7702/EP

**Claims**

1. A nutritional, cosmetic or pharmaceutical composition, which contains as active ingredient, at least one flavanone compound or its derivatives, or a mixture thereof, in an efficient amount to prevent, alleviate or treat skin, hair and/or coat disorders.
2. A composition according to claim 1, wherein the flavanone compounds is isosacuranetin, naringin, hesperidin, eriodictyol, poncirin, neoeriodictin.
3. A composition according to claim 1, wherein the derivatives are the aglycone, chalcone, glycosylated or methylated forms of the flavanone or sulfated and glucuronidated forms which are product of their metabolism in blood.
4. A composition according to claim 1, wherein the derivative is obtained by enzymatic treatment, or synthetically produced.
5. A composition according to any of claims 1 to 4, in which the flavanone compound is extracted from pulp or peel of Citrus fruits such as orange, lemon, bitter orange or grapefruit.
6. A composition according to any of claims 1 to 5, which further contains other active compounds such as vitamin C, vitamin E, carotenoids, ubiquinones, catechins, coffee extracts containing polyphenols and/or diterpenes, extracts of chicory, ginkgo biloba extracts, grape or grape seed extracts rich in proanthocyanidins, spice extracts, soy extracts, other sources of flavonoids with antioxidant activity, fatty acids, prebiotic fibers, probiotic microorganisms, taurine, resveratrol, aminoacids, selenium or precursors of glutathione.
7. A composition according to any of claims 1 to 5, which is milk, yogurt, curd, cheese, fermented milks, milk based fermented products, ice-creams, milk based powders,

NO 7702/EP

infant formulae, cereal products, fermented cereal based products, mineral water, chocolate or pet food, dietary supplement, tablets or cosmetic products for topical application.

- 5        8. Use of at least one flavanone compound or its derivatives, or a mixture thereof, as active ingredient for the preparation of a composition intended to prevent, alleviate or treat skin, hair and/or coat disorders or damages.
- 10       9. Use of at least one flavanone compound or its derivatives, or a mixture thereof, as active ingredient for the preparation of a composition intended to improve skin, hair and /or coat conditions when administered to human or pet animal.
- 
- 15       10. The use according to claim 8 or 9, wherein the flavanone compounds is isosacuranetin, naringin, hesperidin, eriodictyol, poncirin, neoeriocitrin or derivatives selected from their aglycone, chalcone, glycosylated or methylated forms or sulfated and glucuronidated forms which are product of their metabolism in blood.
- 20       11. The use according to any of claims 8 to 10, in which the flavanone compound is extracted from pulp or peel of Citrus fruits such as orange, lemon, bitter orange or grapefruit.
- 25       12. The use according to any of claims 8 to 11, wherein the composition is a cosmetic, nutritional or pharmaceutical composition.
- 30       13. The use according to any of claims 8 to 12, wherein the flavanone compounds, its derivatives or mixtures thereof is present in an amount of from 0.01 mg to 1g, preferably 0.1 mg to 800 mg of aglycone equivalent of the flavanone compound.
14. The use according to any of claims 8 to 13, wherein skin disorders or damages are produced by ageing or a stress situation such as chemical, biological or a physical

NO 7702/EP

stress, exposure to oxidants or carcinogens, to bacteria, viruses, fungi, lipids derived from surrounding cells and/or microbes, or exposure to UV-irradiation.

5 15. The use according to any of claims 8 to 14, in which the composition is intended to improve skin photoprotection, hydration, dryness, firmness, elasticity, oilness, thickness, regular pigmentation, barrier function, skin elasticity, to prevent oxidative status, risks of cancer, inflammation or modulate sebum production or composition, and/or reduce signs of ageing.

10 16. The use according to any of claims 8 to 14, in which the composition is intended to improve hair and coat gloss, hair density, color, oilness, to ameliorate hair fibre diameter, sebum production and to prevent hair and coat loss.

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15 17. The use according to any of claims 8 to 14, in which the flavanone compounds, its derivatives or mixtures thereof is present in an amount of from 0.01 mg to 1g, preferably 0.1 mg to 800 mg of aglycone equivalent of the flavanone compound

NO 7702/EP



**Abstract****Composition for improving skin, hair and coat health.**

- 5 The present invention pertains to a composition for preventing, decreasing and/or treating skin and hair/coat disorders, such as is effected by inflammatory reactions, environmental factors, ageing or cancer. In particular, the present invention relates to the use of flavanones compounds or their derivatives in nutritional, cosmetic or pharmaceutical compositions for improvement of human or pet animal skin and coat conditions.

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NO 7702/EP

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